

**DISERTASI**

**PENGARUH MULTIKOMPONEN KRISTAL PIPERIN  
ASAM NIKOTINAT TERHADAP PROFIL DISOLUSI,  
PROFIL LIPID DAN EKSPRESI GEN PCSK9 DAN  
LDLr PADA TIKUS HIPERLIPIDEMIA**



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## ABSTRAK

### PENGARUH MULTIKOMPONEN KRISTAL PIPERIN ASAM NIKOTINAT TERHADAP PROFIL DISOLUSI, PROFIL LIPID DAN EKSPRESI GEN PCSK9 DAN LDLr PADA TIKUS HIPERLIPIDEMIA

Maria Dona Octavia

Piperin merupakan senyawa metabolit sekunder golongan alkaloid hasil isolasi dari *Piper nigrum*, L, memiliki aktivitas farmakologis, salah satunya aktivitas antihiperlipidemia. Piperin termasuk ke dalam *Biopharmaceutical Classification System* kelas II, yang memiliki kelarutan yang rendah di dalam air sehingga menyebabkan rendahnya bioavailabilitasnya. Penelitian ini bertujuan untuk melihat pengaruh multikomponen kristal piperin asam-nikotinat terhadap sifat fisikokimia, meningkatkan kelarutan, profil disolusi, aktivitas antihiperlipidemia dan ekspresi gen *proprotein convertase subtilin kexin 9* (PCSK9) dan *low density lipoprotein receptor* (LDLr) pada tikus hiperlipidemia.

Multikomponen kristal dibuat dengan metode *solvent drop grinding* menggunakan pelarut etanol *pa* dengan penambahan asam nikotinat sebagai koformer. Multikomponen kristal yang terbentuk dikarakterisasi dengan difraksi sinar-X, *differential scanning calorimetry*, spektroskopi *Fourier Transform-Infra Red*, *scanning electron microscopy*, uji kelarutan dan profil disolusi menggunakan KCKT dengan fase gerak asetonitril: air (90:10). Penilaian aktivitas antihiperlipidemia dilakukan dengan pemeriksaan kadar profil lipid plasma dan ekspresi gen PCSK9 dan LDLr dilakukan dengan *Real Time-Polymerase Chain Reaction*.

Karakterisasi fisikokimia multikomponen kristal menunjukkan penurunan intensitas pada analisa difraksi sinar-X, penurunan puncak endotermik dan nilai entalpi pada termogram DSC, tidak terjadinya interaksi kimia antara piperin dan asam nikotinat pada spektrum FTIR, terbentuknya habit kristal baru pada mikroskopik SEM, kelarutan meningkat sebesar 3,03 kali ( $p < 0,05$ ) dan profil disolusi meningkat 5,92 kali ( $p < 0,05$ ) dibanding piperin murni dan campuran fisika. Aktivitas antihiperlipidemia multikomponen kristal menunjukkan penurunan *total cholesterol*, *total triglyserida*, LDLc ( $p < 0,05$ ) serta meningkatkan HDLc dan Hasil penilaian ekspresi gen menunjukkan pembentukan multikomponen kristal mempengaruhi ekspresi gen PCSK9 dan LDLr.

Multikomponen kristal piperin asam nikotinat dapat memperbaiki sifat fisikokimia, meningkatkan kelarutan, profil disolusi, mempengaruhi kadar profil lipid plasma serta ekspresi gen PCSK9 dan LDLr.

**Kata Kunci:** Piperin, Asam nikotinat, multikomponen kristal, profil disolusi, antihiperlipidemia, PCSK9 dan LDLr

## ABSTRACT

### THE EFFECT OF MULTICOMPONENT CRYSTALS OF PIPERINE-NICOTINIC ACID ON DISSOLUTION PROFILE, LIPID PROFILE AND EXPRESSION OF PCSK9 DAN LDLr GENE IN HYPERLIPIDEMIA RATS

Maria Dona Octavia

Piperine is an alkaloid secondary metabolite compound isolated from *Piper nigrum*, L, which has pharmacological activities, one of which is antihyperlipidemic activity. Piperine is included in the Biopharmaceutical Classification System class II, which has low solubility in water, causing low bioavailability. This study aims to examine the effect of multicomponent nicotinic acid piperine crystals on physicochemical properties, increase solubility, dissolution profile, antihyperlipidemic activity and gene expression of proprotein convertase subtilin kexin 9 (PCSK9) and low-density lipoprotein receptor (LDLr) in hyperlipidaemic rats.

Multicomponent crystals were prepared by the solvent drop grinding method using ethanol pa with the addition of nicotinic acid as a cofomer. The multicomponent crystals formed were characterized by X-ray diffraction, differential scanning calorimetry, Fourier Transform-Infra Red spectroscopy, scanning electron microscopy, solubility testing and dissolution profiles using high performance liquid chromatography with acetonitrile as the mobile phase; water (90:10). Evaluation of antihyperlipidemic activity was carried out by examining plasma lipid profile levels and PCSK9 and LDLr gene expression by Real Time-Polymerase Chain Reaction.

Physicochemical characterization of multicomponent crystals showed a decrease in intensity on X-ray diffraction analysis, a decrease in endothermic peaks and enthalpy values on the DSC thermogram, no chemical interactions between piperine and nicotinic acid in the FTIR spectrum, formation of new crystal habits on SEM microscopy, solubility increased by 3, 03 times ( $p < 0.05$ ) and dissolution profile increased 5.92 times ( $p < 0.05$ ) compared to pure piperine and physical mixture. The antihyperlipidemic activity of multicomponent crystals showed a decrease in total cholesterol, total triglycerides, LDLc ( $p < 0.05$ ) and increased HDLc and gene expression. The results of the assessment of gene expression showed that the formation of multicomponent crystals affected the gene expression of PCSK9 and LDLr.

Multicomponent nicotinic acid piperine crystals can improve physicochemical properties, increase solubility, dissolution profiles, affect levels of plasma lipid profiles and expression of PCSK9 and LDLr genes.

**Keywords:** Piperin, nicotinic acid, multicomponent crystal, dissolution profile, antihyperlipidemia, PCSK9, and LDLr